Respiratory Medicine (2012) **106**, 1071–1081

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REVIEW

Cognitive dysfunction in patients with chronic obstructive pulmonary disease – A systematic review

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Received 4 November 2011; accepted 23 March 2012
Available online 11 May 2012

KEYWORDS
COPD;
Cognitive function;
Neuropsychological tests;
Exacerbation;
Activities of daily living;
Severity of COPD

Summary
Background: Substantial healthcare resources are spent on chronic obstructive pulmonary disease (COPD). In addition, the involvement of patients in monitoring and treatment of their condition has been suggested. However, it is important to maintain a view of self-care that takes differences in cognitive ability into account.

The *aim* of this study was to determine the occurrence and severity of cognitive dysfunction in COPD patients, and to assess the association between severity of COPD and the level of cognitive function.

Methods: We conducted a systematic review, and a search in the following databases: Medline, PsychINFO, Cochrane Library, EMBASE, CINAHL, and SweMed up to July 2010. The articles were included if[1] participants were patients with COPD,[2] relevant outcome was cognitive function investigated by a neuropsychological test battery, and[3] the severity of COPD had been assessed.

Abbreviations: BADL, basic activities of daily living; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume (in the first second), FVC; forced vital capacity, IADL; instrumental activities of daily living, MDB; Mental Deterioration Battery, MMSE; mini mental state examination, MRI; magnetic resonance imaging, $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PICO, participants, interventions, comparisons, outcome; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SaO_2, arterial oxygen saturation of hemoglobin.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2012.03.013

Results: Fifteen studies were included, involving 655 COPD patients and 394 controls. Cognitive function was impaired in COPD patients as compared to healthy controls, but the level of functioning was better than in patients with Alzheimer's disease. There was a significant association between severity of COPD, as measured by lung function and blood gases, and cognitive dysfunction, but only in patients with severe COPD.
Conclusions: Cognitive impairment can be detected in severe COPD patients, but the clinical relevance of the cognitive dysfunction is not yet known. Future studies should concentrate on the consequences of cognitive dysfunction for daily living in these patients, and solutions involving a high degree of self-care might require special support.

Contents

Introduction

Chronic obstructive pulmonary disease (COPD) affects up to 600 million people worldwide and it is currently one of the leading causes of morbidity and mortality in patients suffering from chronic diseases. The prevalence of COPD increases with age, and globally there is a growing number of people who are more than 65 years old,[1] and major healthcare resources are spent on COPD, with 50% of costs accounted for by hospital stays.[2] In addition, the demand for home care services has increased, and patients should be involved in monitoring and treatment of their disease in co-operation with the health professionals.[3]

However, it is important to maintain a view of self-care that takes differences in cognitive ability into account. The literature indicate that cognitive dysfunction could be a limitation in patients with COPD.[4] Therefore, the level of cognitive functioning of these patients must be taken into consideration before self-care can be planned and tailored toward the patient's individual capability and needs.[5]

COPD is not only characterized by progressive and largely irreversible limitation of air flow, shortness of breath, cough, and expectoration.[6] In addition, brain function may be adversely affected by COPD, and magnetic resonance imaging (MRI) has shown altered cerebral perfusion in patients with COPD who have cognitive dysfunction as a clinical manifestation.[7] The relationship between the many processes involved in an everyday cognitive task is complex, but cognitive ability is usually broken down into domains concerning memory, learning ability, attention/concentration, abstract thinking, and problem solving.[4] Cognitive dysfunction reduces the level of functioning as assessed by activities of daily living,[8,9] and it is associated with poor compliance with both medication and oxygen therapy, and poor compliance increases the risk of acute exacerbation.[10,11]

Hypoxemia and hypercapnia appear to aggravate cognitive dysfunction in patients with COPD,[12] and in a multicenter study of 302 patients with mild, moderate and severe hypoxia, the frequency of cognitive dysfunction was 27% in patients with mild hypoxia and 61% in patients suffering from severe hypoxia. Increasing age and low level of education were also associated with cognitive impairment.[13] Furthermore, a direct association between cerebral hypo-perfusion and cognitive dysfunction has been described.[7,14] In addition, cognitive performance might also be affected in patients with normal oxygen saturation.[15] An association has also been described between cognitive impairment and fatigue, and increased need for sleep in patients with severe COPD.[16] Also, McSweeny and colleagues discovered that cognitive dysfunction in patients with COPD was closely related to impaired functioning in daily life.[17]

In a previous systematic review of patients with COPD the authors concluded that these patients may function at a reduced level of cognition, and that cognitive impairment is associated with a lower quality of life depending on the study design, the neuropsychological tests used, and sample size.[4] The review included 81 studies encompassing

multiple psychological characteristics or dimensions, 25 of which included assessments of cognitive function, published between 1966 and 2004. Six out of 25 studies only used the Mini Mental State Examination (MMSE) to evaluate cognitive function, and they found no impairment.[4] However, the MMSE is developed for screening for dementia,[18] and MMSE as a single test might fail to detect more subtle forms of cognitive impairment.[19] In addition, the severity of the disease was only reported in one study. It is therefore difficult to investigate a possible relationship between the severity of COPD and the degree of cognitive dysfunction, and more importantly, the potential consequences for the patient's daily life.

The *aim* of this study was to determine the occurrence and severity of cognitive dysfunction in patients with COPD, based on a systematic review of the literature. Furthermore, we wanted to determine the association between the severity of COPD and the level of cognitive function.

Methods

Search strategy

We adopted a systematic approach based on the guidelines set out by the Centre for Review and Dissemination, University of York (2001),[20] but a systematic search strategy was furthermore initiated based on the PICO (Participants, Interventions Comparisons, Outcome) framework to identify core concepts, facets, and keywords for searching of electronic databases.[21]

The strategy was customized for each database and included controlled vocabulary, such as the National Library of Medicine MeSH and keywords, to identify relevant studies for this review. We systematically searched the following databases: Medline/PubMed, PsychINFO, the Cochrane Library, EMBASE, CINAHL, and SweMed up to July 2010. The search was conducted using the following keywords: COPD, Chronic Obstructive Pulmonary Disease, Pulmonary Disease, Chronic Obstructive [MeSH], Neuropsychological tests [MeSH], Psychomotor Disorders [MeSH], Cognitive function, Cognitive dysfunction, Cognitive impairments, Cognitive performance, and Brain perfusion.

Selection criteria

The selection of studies was done systematically. Following an initial examination of title and abstract, full-text articles were retrieved independently by first and second author for further examination and selection. The reviewers compared their selections of included studies, and any disagreements were discussed and resolved by consensus. The articles were critically evaluated and included in this review if they met the following criteria. 1. Participants were identified as patients with COPD. 2. Relevant outcome was cognitive function, investigated by a neuropsychological test battery, describing memory, attention/concentration, abstract thinking, mental flexibility, and learning ability. 3. The severity of COPD was assessed by lung function and/or blood gases.

Because the aim of this study was to investigate the occurrence of cognitive dysfunction in patients with COPD, we did not include any studies investigating the effect of an intervention. Studies only using the Mini Mental State Examination (MMSE) were excluded because the MMSE has a low sensitivity in relation to slight impairment[18] and the diagnostic accuracy of the instrument has been found to be lower in patients with COPD than in the general population.[22]

The PRISMA checklist (2009) was used to make an attempt to report the results systematically.[23]

Results

The literature search was finalized in July 2010, and we identified a total of 273 abstracts (Fig. 1). Twenty-five additional abstracts were identified through hand searches. A total of 39 full-text articles, published between 1982 and 2009, were identified and 24 studies were excluded. The reasons for exclusion were[1] the use of MMSE as a single test to evaluate the patients' cognitive function (nine studies),[2] investigation of auditory and visually evoked potentials, using a Cadwell Spectrum 32 recording instrument (two studies),[3] using only driving simulator test (one study).[4] no description of COPD severity for the patients included (three studies), and[5] investigation of the effect of different kinds of interventions in relation to COPD (six studies). Two studies were excluded because they were reviews of previously published studies included in this review, and one study was excluded because it was only a protocol. Fourteen original studies (15 references) were included in this review, and nine of them[11,15,16,19,24–28] were included in a former review by Hynninen et al. from 2005.[4] All fourteen studies used a neuropsychological test battery (Table 1).

Of the fifteen studies included in this systematic review, ten were designed as "case-control studies", nine of which included healthy volunteers; three of these studies had mixed control groups and one study only had patients with chronic cerebral vascular disorders as a control group. One study used a prospective cohort design,[12] and the last four studies used descriptive designs.[8,16,25,28] The total numbers of study participants were 655 patients with COPD and 394 controls. Mean age of the study participants was 63.9 years. Information about gender distribution was available for 14 studies, and one study was conducted with males only. The severity of COPD was described in all fifteen studies and ranged from moderate to very severe COPD.

The main content of and methodological details from the relevant articles were extracted and tabulated into a matrix (Table 2), with information organized under the headings: author, year, design, sample (severity of COPD), neuropsychological test instruments used, definition of cognitive dysfunction, occurrence and severity of cognitive dysfunction, and correlation between severity of COPD and cognitive dysfunction.

Occurrence and severity of cognitive dysfunction in patients with COPD

Eight case-control studies found significant impairment in cognitive performance in half of the tests used compared to healthy controls.[7,11,15,19,26,27,29,30] In two case-control

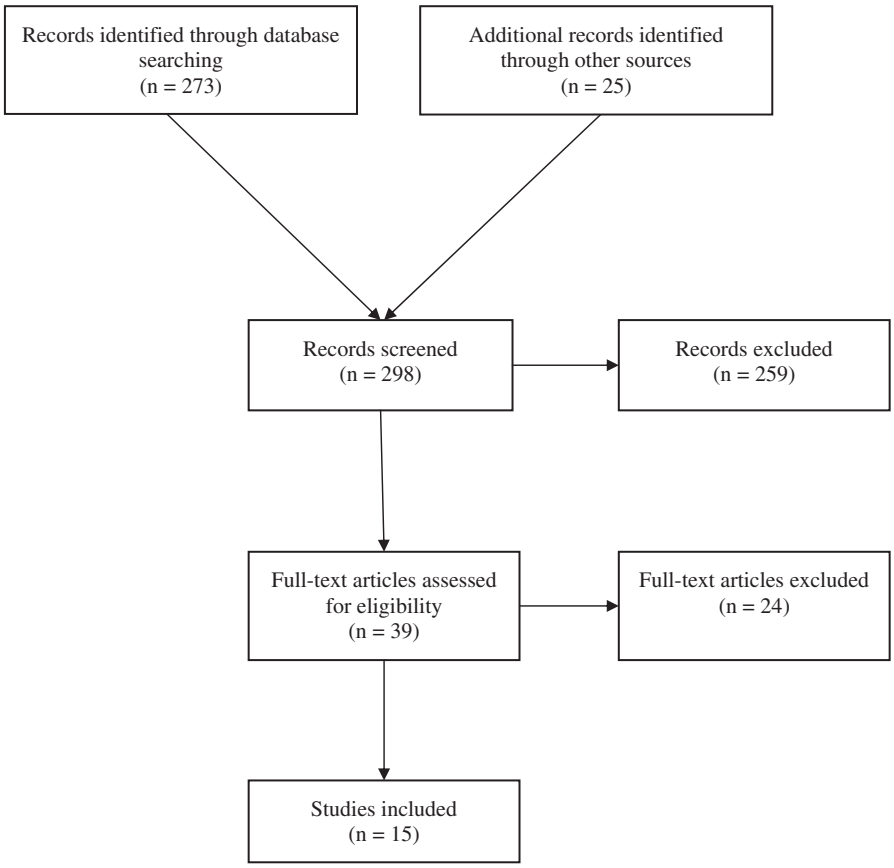

Figure 1 Flow diagram of the inclusion process.

studies, the impairment was not statistically significant.[24,31] The occurrence of cognitive dysfunction in patients with COPD was determined in only two studies[12,26] — to be 17 patients (48.5%) and 13 patients (10.4%) — using the Mental Deterioration Battery, a global battery of tests assessing verbal intelligence, short-term verbal memory, immediate visual-spatial memory, visual-spatial intelligence, and constructional abilities.

With regard to the severity of cognitive dysfunction, three studies compared patients with COPD to patients with Alzheimer disease,[11,19,26] and the patients with COPD performed significantly better in cognitive tests, but the test results from these patients were comparable to data obtained from patients with multi-infarct dementia.[26]

Antonelli-Incalzi et al. found that patients with COPD had a significantly lower level of functioning in one of 13 cognitive tests, namely the "copying drawing with landmarks".[12] In a later study, they found significant differences in cognitive function in five of 12 cognitive tests; visual-spatial intelligence, verbal fluency, short-term verbal memory, copying drawing with landmarks, and immediate visual memory.[8] In the remaining three studies, a mild, cognitive impairment was found that was not statistically significant,[16,25,28] and in two studies the findings were compared with normative data.[16,25]

Regarding cognitive domains, memory[7,8,11,16,24,27,29,31] and attention[7,8,11,15,24,27,30] are shown to be the most influenced domains in most of the studies. Also speed, coordination and learning abilities are affected,[7,15,27] see Table 2.

Relationship between severity of COPD and cognitive dysfunction

The relationship between cognitive dysfunction and severity of COPD was measured in relation to lung function (FEV_1, FEV_1/FVC) and/or blood gases (PaO_2, $PaCO_2$, SaO_2). None of the three studies that included patients with moderate COPD found any significant association with severity of COPD.[19,24,30] In the group of studies investigating patients with severe to very severe COPD (according to GOLD guidelines), eight of 12 studies found that these patients' cognitive impairments were significantly associated with the severity of COPD.[7,15,16,25–29] The remaining four studies found no association between severity of COPD and cognitive dysfunction,[31] or it was not assessed[8,11,12,31]).

Neuropsychological tests used and definition of "cognitive dysfunction"

All 15 studies included a battery of neuropsychological tests. The tests used measured visual and verbal memory (immediate and delayed recall), attention, concentration and speed, visual-spatial intelligence, constructive functions etc. (see Table 1).

A clear theoretical definition of "cognitive dysfunction" that is appropriate for patients with COPD have not been generally accepted. In consequence, different studies use different operational definitions. For example, one author

Table 1 Domains and cognitive tests.

Domain	Cognitive test (name)
Memory and learning	Memory efficiency test
(Immediate memory)	Wechsler memory
(Delayed memory)	scale-revised
(Verbal memory)	VLMT
(Nonverbal memory)	Ray's auditory verbal
(Learning)	memory test
	Story recall
	Selective reminding test
	Mental deterioration battery
Attention	Digit span subtest
(Simple attention)	WRG S5
(Selective attention)	Cognitrone S2
(Sustained attention)	WDG
(Focused attention)	Stroop color word test
Intelligence	ZVT, MWT
	Wechler's adult
	intelligence scale
	Wide range achievement
	test −3
	Groningen intelligence test
Information processing speed and coordination	Trail making test − B
	Halstad−Reitan test
	battery for adults
	TAP
	Grooved pegboard test
	Speech sounds perceptions
	test
	Lafayette repeatable
	test battery
	Finger tapping test
Verbal fluency	Controlled oral word
	association test
	Animal naming test
	Sentence construction
	Aphasia screening test
	Boston naming test
	Animal name fluency test
	Verbal fluency
	Mental deterioration battery
Visual attention	Raven progressive matrices
(Visual-spatial intelligence)	Benton visual retention test
(Visuospatial scanning ability)	Color trail test
(Visual exploration)	Albert's test
	Copying drawings
	Mental deterioration battery
Auditory attention	Seashore rhythm test
Conceptual function	Wisconsin card sorting test

of three articles has defined "cognitive dysfunction" as a defective performance of more than four components of the Mental Deterioration Battery (MDB)".[11,12,26] One study defined cutoff means scores for dementia.[28] The definition used in five other studies was a deterioration of at least one standard deviation (SD) in at least one measure compared to the normative mean.[7,8,16,24,31] In the rest of the remaining six studies included, no specific definition of cognitive dysfunction was given (Table 2).

Discussion

The aim of this review was to determine the occurrence and severity of cognitive dysfunction in patients with COPD. The occurrence of cognitive dysfunction was only reported in two studies, being 48.5%[26] and 10.4%.[12] With regard to the severity of cognitive dysfunction, the finding shows that cognitive function is impaired in patients with COPD as compared to healthy controls. Compared to patients with Alzheimer's disease, patients with COPD performed significantly better,[11,19,26] but the test results from COPD patients were comparable to data obtained from patients with multi-infarct dementia. Alzheimer's disease and multi-infarct dementia are serious brain disorders, and perhaps not the most relevant groups with which to compare patients with COPD. But there is a lack of more useful comparison studies comparing COPD patients with, for example, those with diabetes[32] or chronic heart failure,[33] which also show cognitive impairment.

We were unable to assess the effect of cognitive dysfunction on the daily life of patients with COPD. However, the information about the positioning of patients with COPD between that of the healthy controls and that of patients with Alzheimer's disease illustrates the difficulties experienced by these patients.

We found a significant relationship between the severity of COPD and cognitive dysfunction only in patients with severe to very severe COPD. Patients' cognitive impairments were significantly associated with the severity of COPD. Our findings contrast with the results of a review from 2010,[34] where there was no significant relationship between cognitive impairment and the severity of COPD, but they also included fewer studies with patients with severe to very severe COPD and accepted studies that used MMSE as the only test.

The strength of this review is that we critically evaluated the definitions of "cognitive dysfunction" and the neuropsychological tests used in all the studies included. Furthermore, we compared the results to those in other groups of patients when possible, and not only to those in healthy controls, in order to gain an understanding of the degree of cognitive dysfunction. One limitation of the present review is publication bias, because only published studies were included. Another limitation is that several studies had small sample size, and the severity of COPD is not always well described. The included studies use a large variation in the batteries of cognitive tests, and most of the studies did not present an explicit definition of clinically meaningful effects.

There is a distinct lack of information on the strategies for screening for cognitive impairment in patients with COPD. Only one author discussed the neuropsychological tests that are available for these patients, and in earlier studies,[26,35] this author made an effort to develop and validate existing tests to find a battery of tests that would detect more subtle cognitive difficulties in patients with COPD.

Neuropsychological test batteries consist of many single tests that each gives several variables, either scores or time

Table 2 The studies on cognition and COPD that were included.

Study	Design	Sample: COPD	Cognitive tests	Definition of cognitive dysfunction/Occurrence and severity of cognitive dysfunction	Relationship between severity of COPD and cognitive dysfunction
Fioravanti et al., 1995 [24]	Case-control study	$N = 50$ patients with COPD (Moderate) 50 controls (chronic cerebral vascular disorders)	Memory efficiency test	Definition: Mean below age-matched normal population. About 30% of the COPD patients show memory impairment, which was confined to immediate memory? COPD patients' different aspects of memory scores fell between the normal scores and the more impaired CCVD (control group) scores.	Respiratory parameters and memory efficiency were correlated.
Kozora et al., 1999[18]	Case-control study	$N = 32$ patients with COPD (Moderate) Controls: 31 normal subjects 31 mild Alzheimer	Wechsler memory scale-revised Digit span subtest Trail making test − B Controlled oral word association test Animal naming test Boston naming test	Definition: Not described. In 1 (letter fluency) out of 14 tests, the patients with COPD performed *significantly* worse than patients from the normal controls. COPD patients were *significantly better* than patients with Alzheimer's disease in 13 tests.	No significant correlation.
Orth et al., 2006[30]	Case-control study	$N = 32$ patients with COPD (Moderate) 10 healthy controls	ZVT, MWT VLMT WRG S5 Cognitrone S2 WDG TAP	Definition: Not described. Patient with COPD had *significantly* worse results in 14 out of 20 tests, compared with healthy controls. Domains as intelligence and attention were significantly impaired, while memory, speed and coordination were not.	No significant correlation.
Antonelli-Incalzi et al.,1993[26]	Case-control study	$N = 36$ patients with COPD (Severe) Controls: 49 normal adults 26 Alzheimer 28 Multiinfarct Dementia (MDI)	Mental deterioration battery	Definition: MDB − a "defective performance" of more than four components of the mental deterioration battery. 48.5% of the patients with COPD had cognitive impairment, especially in the memory domain. There was *significant* difference in 14 out of 19 cognitive tests, compared with normal adults. Patients with COPD were comparable to patients with MDI, and better than those with Alzheimer's disease in 13 out of 19 tests.	Cognitive impairment was *significantly* and positively correlated with duration of chronic respiratory failure ($p < 0.05$).
Antonelli-Incalzi et al., 1997[11]	Case-control study	$N = 42$ patients with COPD (Severe, very severe) Controls: 27 normal adult 31 Alzheimer	Mental deterioration battery Ray's auditory verbal memory test Wechler's adult intelligence Scale-Revised	Definition: MDB - a "defective performance" of more than four components of the mental deterioration battery. The global cognitive performance assessed by MDB was *significantly* better than in Alzheimer patients ($p < 0.001$), but *significantly* inferior to that of the remaining two normal groups	Not analyzed.

		26 older normal subjects		($p < 0.0001$). In the rest of the 14 tests, patients with COPD were *significantly* impaired in 6 out of 14 tests, including memory and attention, compared with normal adults, but in 10 out of 14 tests patients with COPD scored *significantly* better than the Alzheimer patients.	
Antonelli-Incalzi et al., 2006[12]	Prospective cohort study	$N = 134$ patients with COPD (Severe) 105 servivors 29 non-survivors	Mental deterioration battery	Definition: MDB - a "defective performance" of more than four components of the mental deterioration battery. The prevalence of overall cognitive impairment, expressed by MDB, was 10.4%. In the subtests, the prevalence of the patients' abnormal performance change between 2 and 40%. The only *significant* test results were the "Copying drawings with landmarks" test, that refers to visual attention ($p < 0.02$).	Not assessed.
Antonelli-Incalzi et al., 2008[8]	Descriptive study	$N = 149$ patients with COPD (Severe). High (H), mid (M) and low (L) level of cognitive function	Raven Progressive matrices Verbal fluency Verbal memory Albert's test Copying drawings Wechsler Sentence construction	Definition: Raw cognitive scores were corrected for age and education and compared with data from a reference population. 52/149 patients (35%) had *significantly* lower cognitive performance in 5 out of 12 tests. Visual attention, verbal fluency and memory were the most affected domains.	Not assessed.
Borson et al., 2008[29]	Case-control study (pilot)	$N = 18$ patients with COPD(Severe, very severe) 9 healthy controls	Wide range achievement test 3 Wechsler memory scale Wechsler adult intelligence scale	Definition: Not described. Patients with COPD differed *significantly* from healthy controls in some of the intelligence ($p < 0.03$) and memory ($p < 0.05$) tests, but not in all.	Lower scores in patients with oxygen-dependent COPD vs. non-oxygen-dependent patients on cognitive measures.
Crews et al., 2001[16]	Descriptive study	$N = 47$ patients with COPD (Severe, very severe)	Wechsler adult intelligence scale Wechsler memory scale Trail marking test Wisconsin card sorting test Selective reminding test	Definition: Test scores were more than one standard deviation (SD) below their respective normative means. In 2 out of 24 cognitive tests, over 52% of the patients with COPD were impaired (Selective Reminding Test — that refers to memory). In all other tests, 0—44% of the patients had impaired cognitive function.	All the patients in this study had end-stage COPD.

(*continued on next page*)

Table 2 (*continued*)

Study	Design	Sample: COPD	Cognitive tests	Definition of cognitive dysfunction/Occurrence and severity of cognitive dysfunction	Relationship between severity of COPD and cognitive dysfunction
Fix et al., 1982[25]	Descriptive study	$N = 66$ patients with COPD (Severe)	Wechsler adult intelligence scale Benton visual retention test Trail marking test Speech sounds perceptions test Stroop color word test Seashore rhythm test	Definition: Not described. Mild, but not significant, cognitive impairment in 6 out of 16 cognitive tests, compared to normal range.	3 out of 13 tests correlated significantly.
Liesker et al., 2004[15]	Case-control study	$N = 30$ patients with COPD (Severe) 20 healthy controls	Stroop color word test Trail making test Story recall Groningen intelligence test Wechsler adult intelligence scale	Definition: Not described. Patients with COPD scored *significantly* worse than healthy controls in 3 (speed and coordination, attention, and intelligence) out of 9 cognitive tests.	Patients with lower FEV_1 (<50% pred.) tended to score worse than those with higher FEV_1 (>50% pred.), but this was only significant in 1 out of 9 tests.
Prigatano et al., 1983[27]	Case-control study	$N = 100$ patients with COPD (Severe) 25 healthy controls	Halstad—Reitan test battery for adults Trail making test Aphasia screening test Wechsler memory scale Wechsler adult intelligence scale Lafayette repeatable test battery	Definition: Not described. In 26 out of 40 cognitive tests, patients with COPD were *significantly* impaired, compared to healthy controls. The most affected domains were; Speed and coordination, memory and learning, intelligence and attention.	Cognitive dysfunction was correlated with resting partial pressure of oxygen.
Shimet al., 2001[31]	Case-control study	$N = 17$ patients with COPD (Severe) 6 hypercapnia/ 11 non-hypercapnia 21 healthy controls	Wechsler Memory Scale-Revised Color Trail test Grooved Pegboard Test	Definition: 2 SDs below the standardized values. Mean values for patients with COPD were below standardized values for all 9 cognitive parameters. But only in three tests (general- and verbal memory, and delayed recall), the COPD patients were 2 SDs below the standardized values.	No significant correlation.
Stuss et al., 1997[28]	Mixed decriptive study	$N = 18$ patients with COPD (Severe)	Dementia rating scale Wechsler adult intelligence scale revised Aphasia screening test Boston naming test Animal Name fluency test Finger tapping test Wechsler memory scale Wisconsin Card sorting test	Definition of dementia: the cutoff mean scores for dementia are 123. In the Dementia Rating Scale, 1 out of 18 patients were below cutoff mean score. In the rest of the 31 tests, there were no significant differences.	Significant relationship between blood gases and cognitive measures of memory and attention capacity.

Ortapamuk et al. 2006 [7]	Case-control study	$N = 18$ patients with COPD (Severe, very severe) (8 hypoxemia/ 10 non-hypoxemia) 10 healthy controls	Mental deterioration battery Wechsler memory scale-revised Color trail test Grooved Pegboard test	Definition: Mean below age-matched normal population. Non-hypoxemic patients with COPD were similar to healthy controls in cognitive performance. Hypoxemic patients performed worse than the two other groups, but the result was only *significant* in 5 ($p < 0.01$) out of 21 tests. The domains were verbal and visual memory, attention, concentration and delayed recall.	Hypoxemic patients showed more deterioration in cognitive performance than non-hypoxemic patients.

measurements. However, when initiating a study, it is necessary to decide which variables should be considered for evaluation of cognitive function,[36] and more importantly the definition of the "dysfunction" and the statistical data analysis methods to be used.

When one examines the literature, the crucial step in finding a significant neurocognitive deficit is in determining the definition itself. The definition of a significant deficit varies, and the lower the threshold of "deficit" is determined to be, the larger number of patients will be that have a deficit.[37] Only the studies by Antonelli-Incalzi and colleagues presented a specific definition of "cognitive dysfunction", which was "defective performance of more than four components of the mental deterioration battery".[11,12,26]

The clinical relevance is also important to discuss. In some of the studies reviewed, only some of several tests was found to be significantly altered. Statistically significant differences between groups may not be clinically relevant, and the consequences are also difficult to evaluate in terms of the patient's daily life, including daily activities, self-care behavior, anxiety, and depression. A difference of just a few seconds in the performance of neuropsychological tests may be statistically significant due to a large study group, but is may be of no clinical importance.[36] In most patients, the deficit may not matter in functional terms. Apparently, many activities of daily living do not require the level of performance called for during neuropsychological testing. The discrepancy between decline in test performance and functional decline is also apparent in the methodological difficulties of defining a cognitive deficit or dysfunction.[38]

Accordingly, it is still not possible to conclude that a detected deficit in cognitive function is related to a clinical disability in performing self-management and self-care.

Only one study, by Antonelli-Incalzi and colleagues (2008), focused on the consequences of the patients' cognitive dysfunction for daily living, as assessed by Basic Activities of Daily Living (BADL) scales and Instrumental Activities of Daily Living (IADL) scales. In this study, with 149 patients with severe COPD in three clusters – a high, middle, or low level of cognitive functioning, based on 11 neuropsychological scores – the authors found an association between cognitive dysfunction and need for support in basic daily activities, such as medication, getting dressed, and managing money. The majority of patients who were enrolled were around 65 years old, and 135 out of 145 patients were men. Overall, there was dependency in at least one BADL domain in 39.6% of patients and in one IADL domain in 65.8% of patients. Altogether, 27.5% were dependent in one or more IADL domains, but not in BADL; from this, the authors concluded that the patients were able to live at home with some support. Altogether, 16.1% were dependent in one to five IADL domains but not in any BADL domain, which corresponds to a greater need for support. Finally, about one in every five patients was dependent on external help in one to five IADL domains and in more than one BADL domain, and needed support for several hours a day.[8]

But the association between cognition and activities are still weak, and a causal relationship has not yet been demonstrated. In COPD patients, IADL are more likely to be affected by deconditioning, systemic inflammation and

dynamic hyperinflation, than cognition. In addition, 135 of the 145 patients were men; this is not comparable with the distribution of these patients in general, where women account for at least 50% of the total.

The most affected cognitive domains in this review were memory and attention, but also speed, coordination and learning abilities were reduced in COPD patient. This impairment might have important clinical and healthcare implications in patients with COPD. Therefore, the level of cognitive functioning of these patients must be taken into consideration before self-care can be planned and tailored toward the patient's individual capability and needs. Cognitive dysfunction could resulting in a risk of acute exacerbation, and reduced function in several basic activities of daily living.[9–11,39] McSweeny and colleagues[17] also found that cognitive dysfunction was more closely related to impaired functioning in daily life than to emotional functioning in patients with COPD. This is in line with Orth et al. who discovered that the frequency of accidents in simulated driving situations is significantly increased in patients with COPD,[40] which might influence future legislation regarding driving licenses.

Conclusions

This systematic review has shown that cognitive function is impaired in patients with COPD as compared to healthy controls, but the level of functioning appears to be better than in patients with Alzheimer's disease.

We found an association between severity of COPD and cognitive dysfunction in patients with severe to very severe COPD.

The clinical importance of the cognitive impairments is hard to gauge due to the heterogeneity of outcome measures and lack of consistent definition of cognitive dysfunction in the reviewed studies. Future studies should concentrate on the consequences of cognitive dysfunction for daily living in these patients. Also, in patients with severe and very severe COPD, solutions involving a high degree of self-care might require special support.

Conflict of interest

The authors report no conflicts of interest to disclose. The authors alone are responsible for the content and writing of the paper. All authors have read and accepted the manuscript.

Acknowledgments

This study was supported financially by "The Tryg Foundation" and "The Health Insurance Foundation" (non-commercial).

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